EXHIBIT 6

# AUSTRALIA

## Patents Act 1990

IN THE MATTER OF
US Patent Application No. 09/446,109
by The University of Queensland

EXHIBIT SMT-6

This is Exhibit SMT-6 referred to in the Statutory Declaration by Stephen Maxwell Taylor

dated 12 MAY 2004

Before me:

Joni Rus

JUSTICE OF THE PEACE No. 82333

A person empowered to witness Statutory Declarations under the laws of the Queensland, Commonwealth of Australia

## Antigen-Induced Arthritis Model

**Introduction:**

Antigen-induced arthritis, first described in 1962, is an established model of RA that involves stimulation of T-lymphocyte reactivity against the immunising antigen (Dumonde and Glynn, 1962; Griffiths, 1992). This model is induced by the immunisation of animals with a protein antigen (mBSA, ovalbumin or fibrin) and an adjuvant, followed by the intra-articular injection of the same antigen (Dumonde and Glynn, 1962; Brackertz *et al.*, 1977; Yoshino, 1996; Simon *et al.*, 2001). This results in an immune-complex mediated inflammatory response, characterised by chronic synovitis, which is localised to the injected joint. The ability to localise inflammation to the antigen-injected joint only (monoarticular arthritis) allows for an internal control in the contra-lateral joint (Griffiths, 1992). Many of the disease pathologies in this model mimic those seen in human RA (Table 1), having both acute and chronic phases of disease (Griffiths, 1992). There is also the capacity to induce subsequent flare-ups (as seen in RA), through the re-injection of the antigen (Griffiths, 1992; Goodfellow *et al.*, 1997).

**Table 1:** Animal models of rheumatoid arthritis: relevance to human condition.

| Disease Model | Similarities to human disease |
|---|---|
| **Antigen-Induced (Monoarticular) Arthritis** | - Infiltration of PMNs, macrophages and T-lymphocytes<br>- Swelling of affected joint<br>- Hyperplasia of synovial membrane and synovitis<br>- Cytokine involvement in various stages of disease<br>- Tissue remodeling<br>- Similar histology: cartilage erosions and pannus formation<br>- Induction of flare-up reaction (local T-cell hyperreactivity)<br>- Immune-complex mediated<br>- Complement involvement<br>- Drug responsiveness |
| **Adjuvant Arthritis** | - Polyarthropathy of the small peripheral joints and edema<br>- Unknown autoantigen<br>- Osteoclast involvement<br>- Tissue remodeling and fibrosis<br>- Similar histology: bone erosions and pannus formation<br>- Complement involvement<br>- Drug responsiveness |
| **Collagen-Induced Arthritis** | - Polyarthropathy of the small peripheral joints<br>- Synovitis and periarticular inflammation<br>- Infiltration of PMNs and mononuclear cells<br>- Significant cytokine involvement<br>- Tissue remodeling<br>- Similar histology: bone and cartilage erosions, and pannus formation<br>- Specific MHC association<br>- Immune-complex deposition within joint<br>- Complement involvement<br>- Drug responsiveness |

Information from Johnson *et al.*, 1986; Griffiths, 1992; Griffiths *et al.*, 1992; Griffiths *et al.*, 1995; Yoshino, 1996; Goodfellow *et al.*, 1997; Myers *et al.*, 1997; Williams, 1998; Bendele *et al.*, 1999; Joe *et al.*, 1999; Linton & Morgan, 1999; Goodfellow *et al.*, 2000; van den Berg, 2000; Mizuno *et al.*, 2000.

**Methods:**

Female Wistar rats (225-275g) were obtained from the CABH (Pinjarra Hills, The University of Queensland). Methylated bovine serum albumin (mBSA; Sigma, USA) was suspended in Freund's complete adjuvant (Sigma, USA) at the concentration of 1 mg/mL and sonicated for 10 min to ensure homogeneity. Rats were sensitised to the mBSA by the subcutaneous injection of 0.5 mL of this solution into the hind flanks 2 and 3 weeks prior to challenge (Days –21 and –14). Two weeks after the second injection (Day 0), rats were anaesthetised with ketamine (80 mg/kg i.p.) and xylazine (12 mg/kg i.p.) and both hind legs shaved. A homogenous suspension of 0.5 mg mBSA in 100 $\mu$L saline was aseptically injected into the joint space of the right knee, with the contra-lateral left knee receiving 100 $\mu$L saline alone. Sham-operated rats received 100 $\mu$L saline in both the left and right knees. Rats were then allowed to recover after being placed in separate cages. In the first study, rats were examined for 14 or 28 days after mBSA injection (Day +14 or +28) before being euthanased under anaesthesia prior to sample collection. In the second study, on Day 28 rats were re-anaesthetised with ketamine (80 mg/kg i.p.) and xylazine (12 mg/kg i.p.) and 0.5 mg mBSA in 100 $\mu$L saline was again aseptically injected into right knee joint space, with the contra-lateral left knee receiving 100 $\mu$L saline. These rats were examined for a further 21 days (Day +49) before sample collection following euthanasia under anaesthesia.

The body weight of rats in the 28-day study was measured periodically throughout the experiment. Results are expressed as the change in body weight following mBSA challenge on Day 0.

Right and left knee swelling were quantitatively assessed at various time points during the study period by measuring the medial-lateral width across the joint of

constrained rats with vernier calipers. Results are expressed as the change in left or right knee swelling following mBSA challenge on Day 0, or as a change from Day 4 for rats treated from Day 4-28 with the C5a receptor antagonist.

The appearance of each rat's gait was also scored during the study on a scale of 0-4 as described below.

| Score | Description |
|---|---|
| 0 | No limp, full weight-bearing on hind right leg. |
| 1 | Mild limp. |
| 2 | Moderate limp. |
| 3 | Severe limp. |
| 4 | No weight-bearing on hind right leg. |

At the completion of the 14 and 28-day study, the left and right knee joints of rats were lavaged with 100 $\mu$L saline. The number of total cells in this lavage fluid was then determined using a haemocytometer. Differential cell counts were then performed on air-dried glass smears of lavage samples stained with Wright's stain (Sigma, USA). Red blood cells were excluded from the cell counts and the total number of macrophages, PMNs and lymphocytes was expressed as the number of cells/mL lavage fluid.

Levels of TNF-$\alpha$ were measured in the serum and intra-articular knee lavage samples collected from rats at the completion of the study. An enzyme-linked immunoabsorbant assay (ELISA) antibody set (OptEIA, Pharmingen, USA) was used according to manufacturer's instructions to measure these TNF-$\alpha$ levels. A 96-well round-bottomed immunosorbant plate (Nunc Maxisorb, USA) was coated with 100 $\mu$L rabbit anti-rat TNF-$\alpha$ antibody (capture antibody) diluted 1:200 with coating buffer (0.1 M carbonate,

pH 9.5) and incubated overnight at 4°C. The plate was then washed 3 times with phosphate buffered saline (PBS) containing 0.05% Tween-20 (PBS-Tween) and 200 μL of PBS with 10% fetal calf serum added to each well. Following a 1 hour incubation period, the plate was washed 5 times with PBS-Tween and 100 μL samples added in duplicate. Recombinant rat TNF-α was diluted from 4000 ng/ml to 30 pg/ml and added in duplicate to each plate to serve as a standard curve. The plate was then incubated for a further 2 hours at 37°C followed by 5 washes in PBS-Tween. Diluted biotinylated anti-rat TNF-α monoclonal antibody (detection antibody, 100μL) was then added to each well and the plate incubated at RT for 1 hour. The plate was then washed 5 times with PBS-Tween and 100 μL of avidin-horseradish peroxidase conjugate (enzyme reagent) added to each well. After a 30 min incubation period at RT, the plate was washed 7 times with PBS-Tween and 100 μL of substrate (tetramethylbenzidine) added to each well. Colour was allowed to develop in the dark over 30 min followed by addition of 50 μL of 0.5 M $H_2SO_4$ (stop solution). Absorbance was read at 450 nm and concentrations of TNF-α determined by linear regression analysis from the standard curve. Serum and intra-articular fluids obtained as described in previous sections were stored at -20°C and samples were analyzed within 2 weeks of collection. Results are expressed as ng/g tissue.

After the completion of each study and following the lavaging of knees, the knee joints from every rat were dissected out and then stored in 10% buffered formalin for at least 10 days. Knee samples were then decalcified in a saturated solution of ethylenediaminetetraacetic acid (EDTA) for 21 days. They were then embedded in paraffin wax and sections were cut, mounted and stained using a haematoxylin and eosin stain. Each

section was then scored by Dr. Ian Shiels in a blinded fashion and scored for the level of joint damage in a scale from 0-4 as described below.

| Score | Description |
|---|---|
| 0 | No abnormalities. |
| 1 | Mild inflammatory cell infiltration in the synovial membrane with no significant thickening of the membrane or cartilage erosion. |
| 2 | Extensive inflammatory cell infiltration and mild thickening of the synovial membrane. |
| 3 | Extensive inflammatory cell infiltration and synovitis, thickening and fibrosis of the joint capsule and cartilage involvement without erosions. |
| 4 | Extensive inflammatory cell infiltration and synovitis, significant thickening and fibrosis of the joint capsule and involvement of the articular cartilage with erosions. |

Representative histological sections of each of these scores are shown in Figure 2.1 under 40 x magnification.

A 14- and 28-day (single antigen injection) or 49-day (two antigen injections) study period were used to examine the therapeutic effects of the C5a antagonist on mBSA-induced monoarticular arthritis. The following groups of rats were used in the 14-day study: sham-operated (baseline controls), untreated (arthritis controls), C5a antagonist-pre-treated (1 mg/kg/day), C5a antagonist-post-treated (1 mg/kg/day), and ibuprofen-post-treated (30 mg/kg/day). The following groups of rats were used in the 28-day study: sham-operated (baseline controls), untreated (arthritis controls), C5a antagonist-pre-treated (1 and 0.3 mg/kg/day), ibuprofen-pre-treated (30 mg/kg/day), C5a antagonist (1 mg/kg/day) and

ibuprofen (30 mg/kg/day)-pre-treated combination, and C5a antagonist-post-treated (3 mg/kg/day). Rats that were pre-treated received drug treatment 2 days prior to arthritis induction (Day –2) and then daily throughout the study. Rats that were post-treated received drug treatment 4 days after the induction of arthritis (Day +4) and then daily throughout the study. In the 49-day study, a further 2 groups were examined: untreated rats, and C5a antagonist-pre-treated rats (1 mg/kg/day). In both studies, various parameters were measured in each group at regular intervals over the course of the study.

**Results:**

**14-day study.** Measurements of the saline-injected left knee of each rat did not significantly change from pre-injection values during the course of each experiment (data not shown). Following the injection of mBSA at Day 0 in drug-free sensitized rats, the average increase in the width of the right knee peaked at Day +3 (+4.69 ± 0.32 mm, n = 11; Figure 1A). Rats which had been pretreated from Day –2 with AcF-[OPdChaWR] (1 mg/kg/day), had significantly reduced right knee widths from Days +2-14 (peak at Day +3: +2.08 ± 0.59 mm, n = 9; $P < 0.05$) compared to drug-free arthritic knees (Figure 1A). Gait scores in drug-free arthritic rats also increased above baseline levels following induction of arthritis (Figure 1B). Pretreatment with the C5a antagonist significantly decreased these scores from Days +2-14 ($P < 0.05$). There was a high correlation between gait scores and knee swelling in drug-free arthritic rats for all 3 experimental trials (14 day trial: $r^2 = 0.83$, n = 7; 28 day trial: $r^2 = 0.96$, n = 11; 49 day trial: $r^2 = 0.84$, n = 17) for Days +2 to completion of study.

In a separate study, the effects of the C5a antagonist or ibuprofen on knee swelling and gait scores following the establishment of arthritis were examined. Rats treated with either AcF-[OPdChaWR] (1 mg/kg/day) or ibuprofen (30 mg/kg/day) from Days +2-14, had significantly reduced knee swelling (Days +3-14) and gait scores (Days +4-14) compared to arthritic rats which received no drug treatment ($P < 0.05$; Figure 1C/D).

In the initial 14-day study, TNF$\alpha$ and IL-6 levels were found to be elevated in the right knee lavage fluid on Day 14, as were TNF$\alpha$ levels in the serum of drug-free arthritic rats (Figure 2A/B). Rats pretreated with the C5a antagonist had significantly lower levels of these cytokines ($P < 0.05$; Figure 2A/B) in the joint and serum at Day 14. The majority (>90%) of cells recovered from the right knee lavage fluid at Day 14 were PMNs. Significantly fewer PMNs were found in the lavage fluid of rats treated with AcF-[OPdChaWR] or ibuprofen throughout the study, or in rats treated with the C5a antagonist from Day +2, compared to drug-free arthritic rats ($P < 0.05$; Figure 2C).

The saline-injected left knees of all rats in every study showed no histological abnormalities (Figure 3A) and all were scored 0 (data not shown). Sections from the right knees of drug-free arthritic rats on Day 14 had marked cellular infiltration, which were predominantly neutrophils, and mild synovial cell proliferation, with an average histopathology score of $3.2 \pm 0.3$ ($n = 16$, Figure 2D). Histological sections from rats pretreated with AcF-[OPdChaWR] had a lesser degree of cellular infiltration and synovial proliferation, resulting in a significantly lower histopathological score of $1.4 \pm 0.5$ ($n = 8$; $P < 0.05$; Figures 2D). Histological sections from rats post-treated with the C5a antagonist, 2 days after the induction of arthritis, also had a lower degree of cellular infiltration and synovial proliferation compared to drug-free arthritic rats, although to a lesser extent than

rats pretreated at Day –2 with the C5a antagonist. The mean histopathological scores from these post-treated rats was 2.2 ± 0.4 which was significantly lower than drug-free arthritic rats (n = 8; $P < 0.05$; Figure 2D). In contrast, histological sections from rats treated with ibuprofen (30 mg/kg/day) from Days +2-14, had no change in histological parameters compared to drug-free arthritic rats (score of 3.5 ± 0.3; n = 6; Figures 2D).

**28-day study.** Following arthritis induction, right knee widths of drug-free arthritic rats rapidly increased above baseline to peak at Day +3 (+4.98 ± 0.39 mm above baseline; n = 14) and slowly decreased to +0.51 ± 0.21 mm at Day 28 (Figure 3A). Rats pretreated with AcF-[OPdChaWR] (1 mg/kg/day) from Day –2, had significantly lower right knee widths from Days +1-28 (peak at Day +3: +2.66 ± 0.52 mm, n = 12; $P < 0.05$; Figure 3A). Rats pretreated with AcF-[OPdChaWR] at 0.3 mg/kg/day, also had significantly lower right knee widths from Days +2-15 ($P < 0.05$; Figure 3A). Rats pretreated with ibuprofen (30 mg/kg/day) had significantly decreased knee widths from Days +2-8 only (peak at Day +3: +2.30 ± 0.30 mm; n = 11; $P < 0.05$; Figure 3A). Rats receiving a combination of the C5a antagonist (1 mg/kg/day) and ibuprofen (30 mg/kg/day) from Day –2, had a significant reduction in right knee widths from Days +1-28 (peak at Day +3: +2.19 ± 0.06mm, n = 12; $P < 0.05$; Figure 3A), which was comparable to rats receiving the C5a antagonist alone. Gait scores in rats pretreated with either the C5a antagonist, ibuprofen or the combination of both were significantly reduced compared to drug-free arthritic rats from Days +1-12 ($P < 0.05$; Figure 3B).

In the 14-day studies, which were performed first in the series of studies reported here, the C5a antagonist was administered at 1 mg/kg/day both as a preventative (Days –2-14) and reversal (Days +2-14) therapy. It was noted that rats treated with the antagonist at

this dose from Day +2 had less improvement in histopathological scores compared to rats treated from Day –2 (Figure 2D). In the following 28-day reversal studies, a higher dose of C5a antagonist (3 mg/kg/day) was used to determine if this might be a more effective reversal dose regimen. It was found that rats that were treated with this dosage regime had significantly improved right knee widths (Days +5-28) and gait scores (Days +5-12) compared to drug-free arthritic rats ($P < 0.05$; Figure 3C/D).

In all rats in the 28-day studies, there were no detectable levels of TNFα, either in the serum or in the knee lavage fluid, at Day 28. The vast majority (>95%) of cells recovered in the lavage fluid of the right knees of rats were macrophages. Drug-free arthritic rats had an average of 46.5 ± 12.3 x 104 macrophages/mL lavage fluid (n = 10; Figure 5A), an ~20-fold increase over saline-injected left knees. Rats pretreated with AcF-[OPdChaWR], ibuprofen or a combination of both, or rats treated from Day +4 with the C5a antagonist alone, had significantly lower numbers of macrophages in the right knee lavage fluid (Figure 4A).

Right knee histology from arthritic drug-free rats had varying degrees of synovial cell proliferation and cellular infiltration, and these were scored overall with an average of 2.9 ± 0.3 (n = 16; Figure 4B). Sections from rats either pretreated with C5a antagonist (1 mg/kg/day) or treated from Day +4 (3 mg/kg/day), had an equal reduction in severity of lesions compared to drug-free arthritic rats, with significantly decreased scores of 1.0 ± 0.4 and 1.1 ± 0.5, respectively (n = 12 in each group; $P < 0.05$; Figure 4B). Conversely, rats pretreated with ibuprofen (30 mg/kg/day) had no improvement of right knee pathology, with an average score of 2.9 ± 0.3 (n = 6; Figure 4B). Rats pretreated with a combination of the C5a antagonist and ibuprofen also had a significant reduction in histopathological

scores, which was similar to that of rats treated with only the C5a antagonist (n = 12; Figure 4B).

**49-day study.** In drug-free rats following the first injection of mBSA at Day 0, the right knee increased in width with a peak swelling above baseline of +5.27 ± 0.56 mm (n = 6) on Day +3. Following the second injection of mBSA on Day 28, the increase in the width of the right knee was similar in magnitude to the first challenge, with a peak of +4.47 ± 0.60 mm above pre-injection values, 1 day after the second injection (Figure 5A). Rats pretreated with AcF-[OPdChaWR] at 1 mg/kg/day had significantly lower right knee widths compared to drug-free rats, from Days +1-49 with peaks of +2.87 ± 0.51 (Day 3) and +2.64 ± 0.37 mm (Day 29) for the first and second injection, respectively (n = 6; $P < 0.05$; Figure 5A). Gait scores increased in drug-free arthritic rats with the deterioration in gait proportional to right knee widths, with maximum gait scores following both the first and second injection (Figure 5B). C5a antagonist-dosed rats had significantly improved gait scores from Days +2-16 and +30-44 ($P < 0.05$; Figure 5B).

Examination of right knee sections from 49-day arthritic drug-free rats showed a more severe pathology than was seen in the other studies involving single intra-articular injection of antigen and more limited experimental time spans. All antigen-injected right knees in drug-free rats had marked inflammatory cell infiltration and severe synovial proliferation and fibrosis. Additionally, cartilage erosion was observed in all sections from challenged right knees, resulting in the average histopathological score of 3.9 ± 0.1 (n = 6, Figure 5C). Sections of right knees from rats which had been pretreated with AcF-[OPdChaWR] (1 mg/kg/day) from Days –2 onwards, had decreased pathology compared to drug-free arthritic rats, with a significantly improved score of 1.7 ± 0.7 (n = 6; Figure 5C).

**FIGURE 1.**

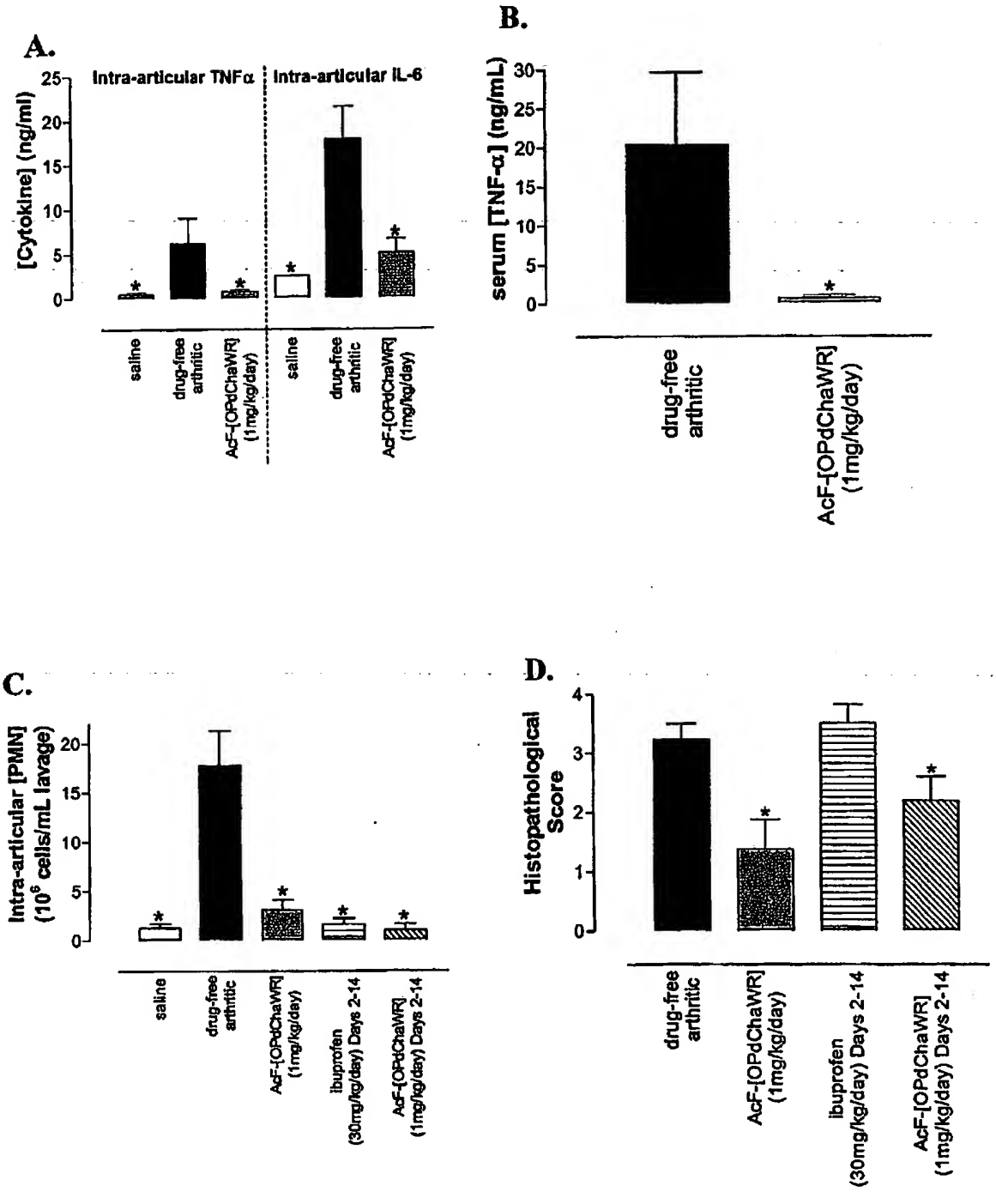

A.
Intra-articular TNFα
Intra-articular IL-6
[Cytokine] (ng/ml)
25
20
15
10
5
0
saline
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
saline
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
B.
serum [TNF-α] (ng/mL)
30
25
20
15
10
5
0
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
C.
Intra-articular [PMN] ($10^6$ cells/mL lavage)
20
15
10
5
0
saline
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
ibuprofen (30mg/kg/day) Days 2-14
AcF-[OPdChaWR] (1mg/kg/day) Days 2-14
D.
Histopathological Score
4
3
2
1
0
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
ibuprofen (30mg/kg/day) Days 2-14
AcF-[OPdChaWR] (1mg/kg/day) Days 2-14

FIGURE 2

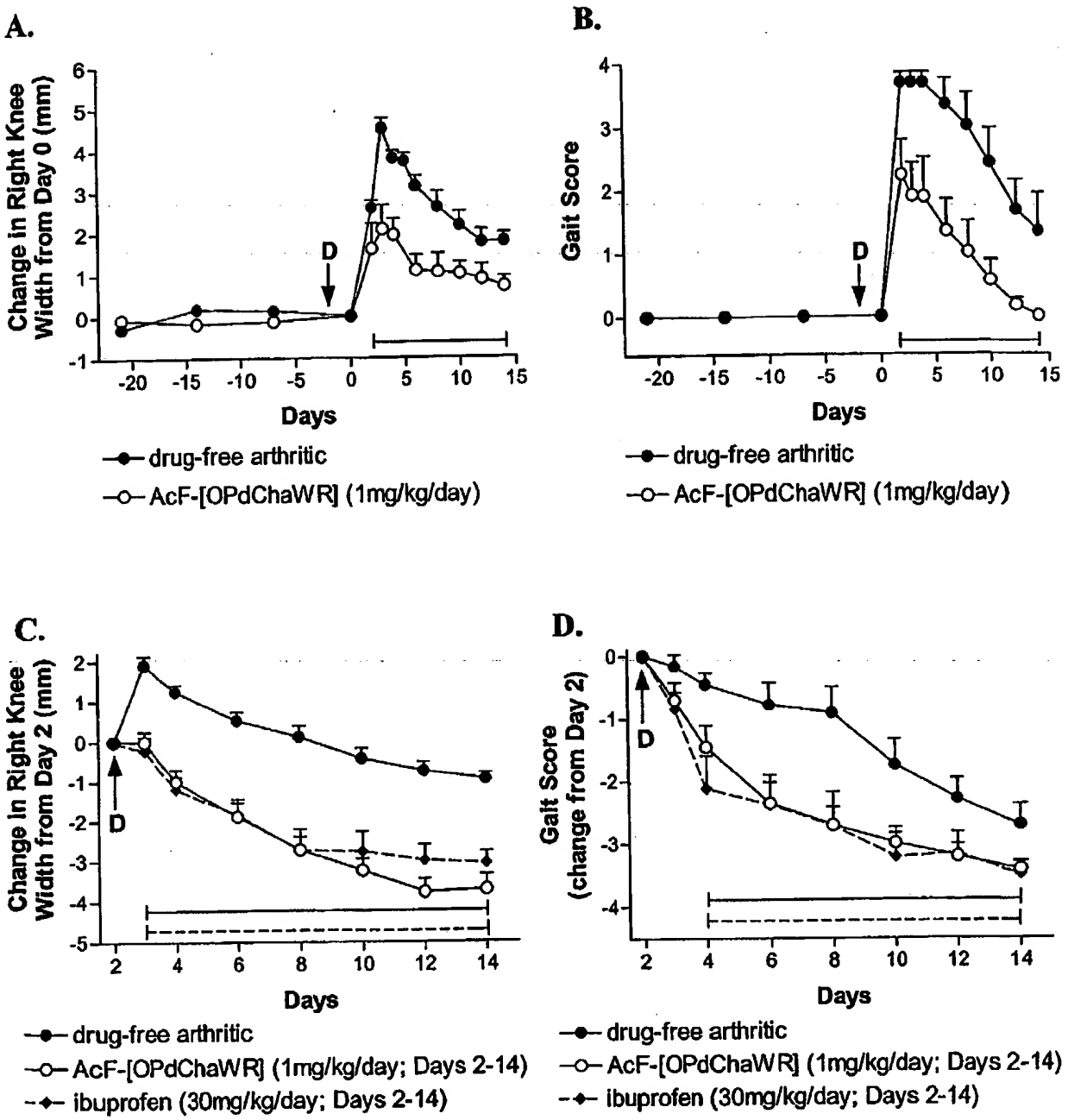

A.
Change in Right Knee Width from Day 0 (mm)
D
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
B.
Gait Score
D
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
C.
Change in Right Knee Width from Day 2 (mm)
D
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day; Days 2-14)
ibuprofen (30mg/kg/day; Days 2-14)
D.
Gait Score (change from Day 2)
D
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day; Days 2-14)
ibuprofen (30mg/kg/day; Days 2-14)

FIGURE 3.

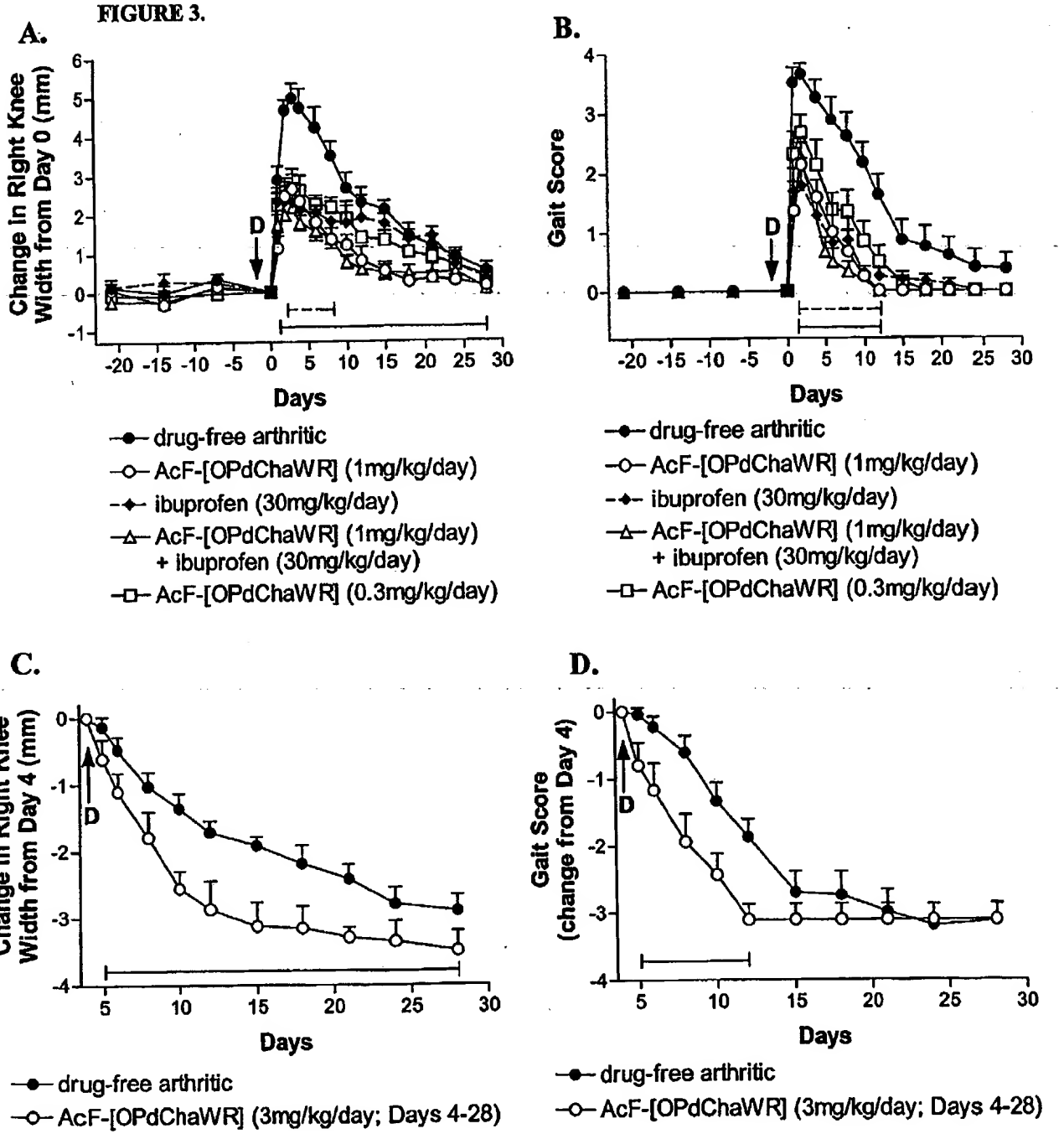
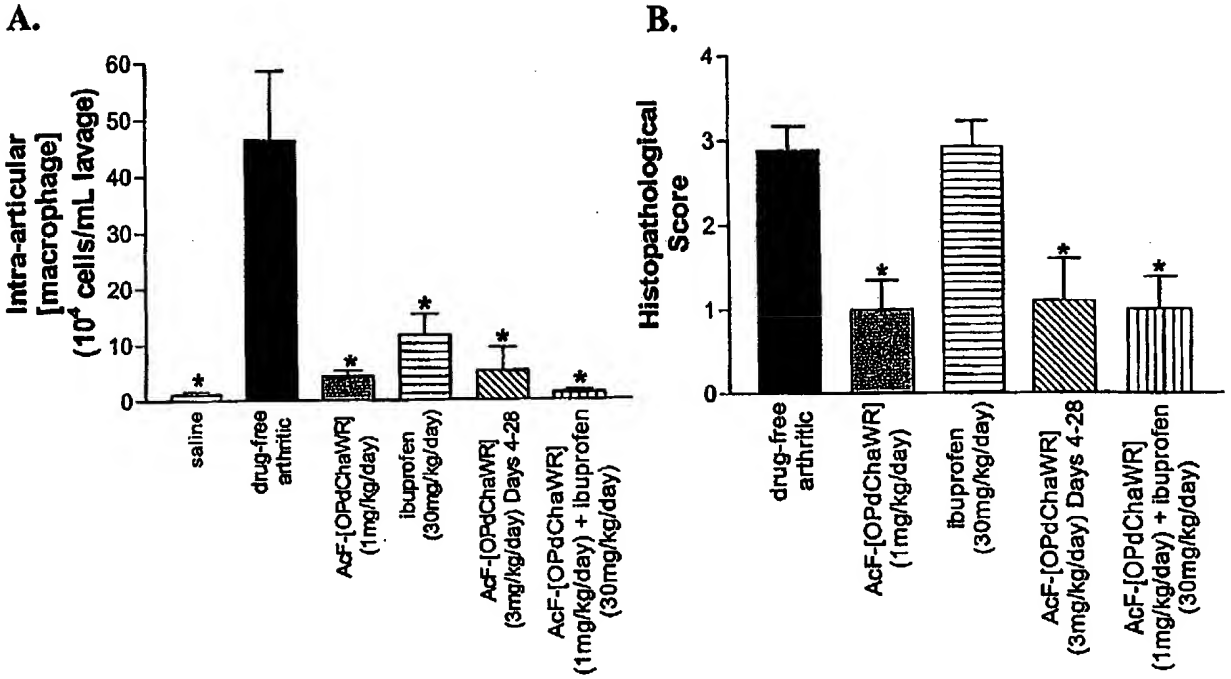

A.
Change in Right Knee Width from Day 0 (mm)
D
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
ibuprofen (30mg/kg/day)
AcF-[OPdChaWR] (1mg/kg/day) + ibuprofen (30mg/kg/day)
AcF-[OPdChaWR] (0.3mg/kg/day)
B.
Gait Score
D
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
ibuprofen (30mg/kg/day)
AcF-[OPdChaWR] (1mg/kg/day) + ibuprofen (30mg/kg/day)
AcF-[OPdChaWR] (0.3mg/kg/day)
C.
Change in Right Knee Width from Day 4 (mm)
D
Days
drug-free arthritic
AcF-[OPdChaWR] (3mg/kg/day; Days 4-28)
D.
Gait Score (change from Day 4)
D
Days
drug-free arthritic
AcF-[OPdChaWR] (3mg/kg/day; Days 4-28)

FIGURE 4.


A.
Intra-articular [macrophage] ($10^4$ cells/mL lavage)
60
50
40
30
20
10
0
saline
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
ibuprofen (30mg/kg/day)
AcF-[OPdChaWR] (3mg/kg/day) Days 4-28
AcF-[OPdChaWR] (1mg/kg/day) + ibuprofen (30mg/kg/day)
B.
Histopathological Score
4
3
2
1
0
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
ibuprofen (30mg/kg/day)
AcF-[OPdChaWR] (3mg/kg/day) Days 4-28
AcF-[OPdChaWR] (1mg/kg/day) + ibuprofen (30mg/kg/day)

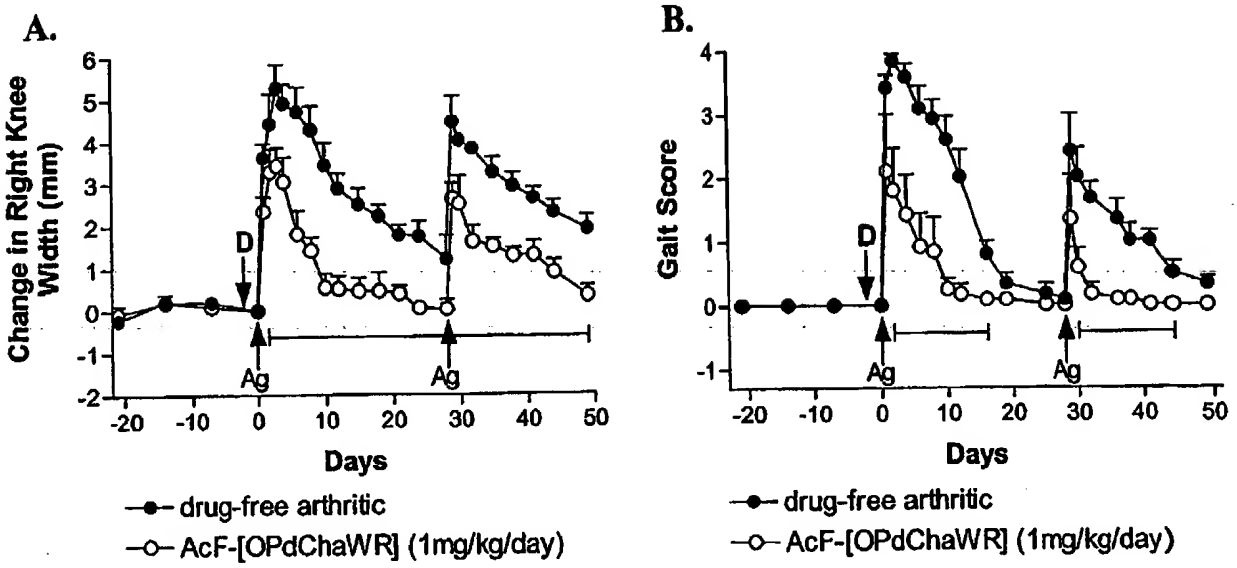
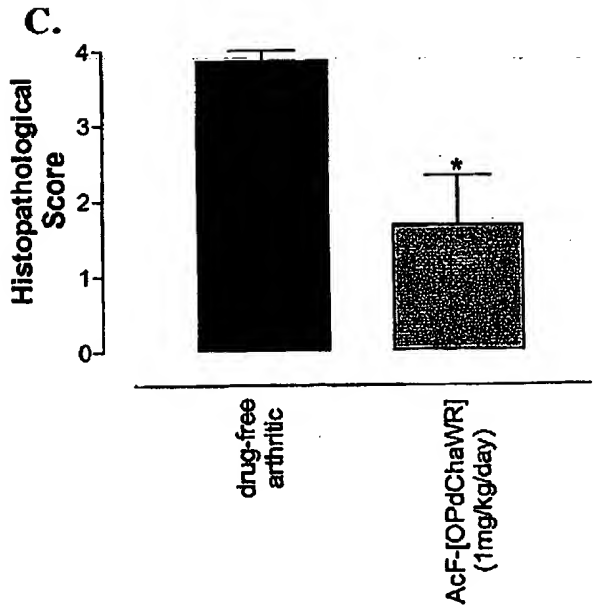

A.
Change in Right Knee Width (mm)
D
Ag
Ag
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)
B.
Gait Score
D
Ag
Ag
Days
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)

FIGURE 5.


C.
Histopathological Score
*
drug-free arthritic
AcF-[OPdChaWR] (1mg/kg/day)

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